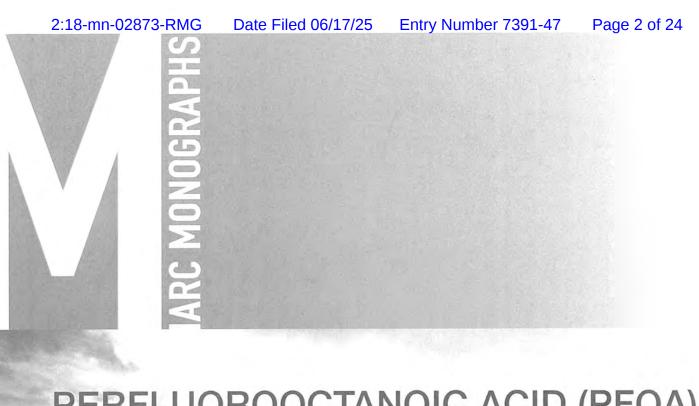
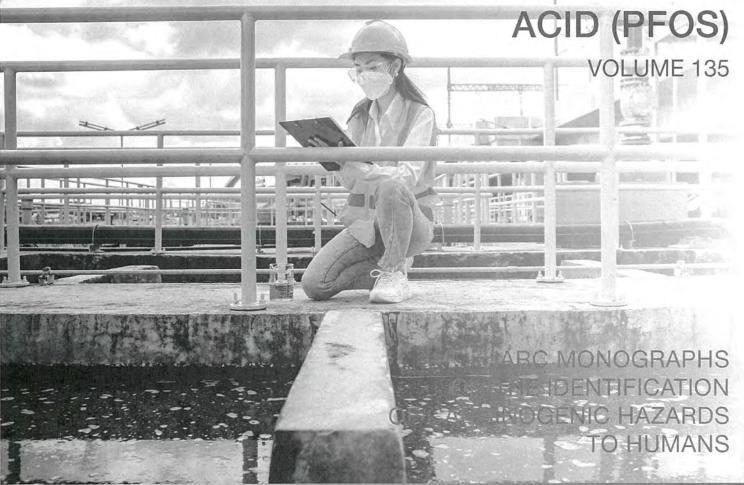
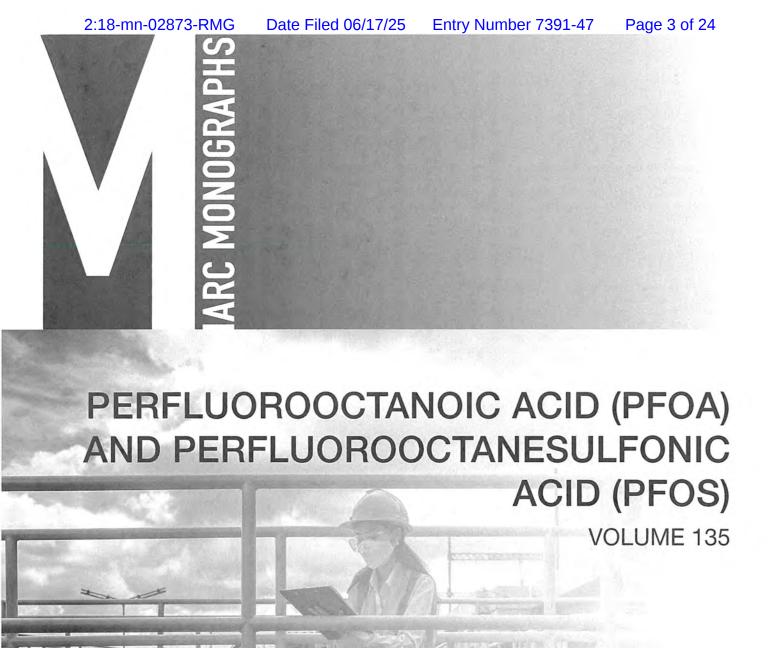
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International Agency for Research on Cancer



This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 7–14 November 2023

LYON, FRANCE - 2025

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic hazard of chemicals to humans, involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic hazards associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of cancer hazard to humans with the help of international working groups of experts in carcinogenesis and related fields; and to identify gaps in evidence. The lists of IARC evaluations are regularly updated and are available on the internet at https://monographs

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About the cover: Worker at a wastewater treatment plant. PFOA and PFOS are ubiquitous in the environment and may contaminate drinking-water.

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NOTE TO THE READER

The evaluations of carcinogenic hazard in the *IARC Monographs on the Identification of Carcinogenic Hazards to Humans* series are made by international working groups of independent scientists. The *IARC Monographs* classifications do not indicate the level of risk associated with a given level or circumstance of exposure. The *IARC Monographs* do not make recommendations for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic hazard of an agent to humans is encouraged to make this information available to the *IARC Monographs* programme, International Agency for Research on Cancer, 25 avenue Tony Garnier, CS 90627, 69366 Lyon Cedex 07, or via email at imp@iarc.who.int, in order that the agent may be considered for reevaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the *IARC Monographs* programme. Corrigenda are published online on the relevant webpage for the volume concerned (IARC Publications: https://publications.iarc.who.int/).

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⁴ Each Observer agreed to respect the Guidelines for Observers at *IARC Monographs* meetings. Observers did not serve as Working Group members, draft any part of a monograph, or participate in the evaluations. They also agreed not to contact participants before the meeting, not to lobby them at any time, not to send them written materials, and not to offer them meals or other favours. IARC asked and reminded Working Group members to report any contact or attempt to influence that they may have encountered, either before or during the meeting.

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6. EVALUATION AND RATIONALE

6.1 Cancer in humans

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There is limited evidence in humans for the carcinogenicity of perfluorooctanoic acid (PFOA). Positive associations have been observed between PFOA and renal cell carcinoma and cancer of the testis.

There is inadequate evidence in humans regarding the carcinogenicity of perfluorooctanesulfonic acid (PFOS).

6.2 Cancer in experimental animals

There is sufficient evidence in experimental animals for the carcinogenicity of PFOA.

There is limited evidence in experimental animals for the carcinogenicity of PFOS.

6.3 Mechanistic evidence

There is strong evidence that PFOA exhibits multiple key characteristics of carcinogens in exposed humans, in human primary cells, and in experimental systems.

There is strong evidence that PFOS exhibits multiple key characteristics of carcinogens in exposed humans, in human primary cells, and in experimental systems.

6.4 Overall evaluation

PFOA is carcinogenic to humans (Group 1). PFOS is possibly carcinogenic to humans (Group 2B).

6.5 Rationale

6.5.1 PFOA

The Group 1 evaluation for PFOA is based on the combination of sufficient evidence for cancer in experimental animals and strong mechanistic evidence of key characteristics of carcinogens in exposed humans. The evidence for cancer in experimental animals was sufficient because exposure to PFOA caused an increase in the incidence of an appropriate combination of benign and malignant neoplasms in both sexes of a single species (rat) in one study that complied with GLP. The mechanistic evidence was strong in exposed humans because PFOA induces epigenetic alterations and is immunosuppressive. In exposed humans, PFOA induces epigenetic alterations in the form of gene-specific methylation and cancer-related miRNAs. These effects are supported by evidence of epigenetic alterations in multiple experimental systems. In exposed humans, PFOA is immunosuppressive, increasing risk of infectious disease and decreasing vaccine response to diverse antigens. These effects are supported by evidence

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of immunosuppression in human primary cells and experimental systems. In addition, in human primary cells and experimental systems, PFOA induces oxidative stress and modulates receptor-mediated effects. Additionally, in experimental systems, PFOA alters cell proliferation, cell death, or nutrient supply.

Also, for PFOA, the evidence for cancer in humans was found to be limited for renal cell carcinoma and cancer of the testis. Despite the increase in the number of available human cancer studies since the previous evaluation by the IARC Monographs, the results were somewhat inconsistent across the studies. For renal cell carcinoma, positive findings were observed in three studies conducted in partly overlapping occupationally and environmentally exposed populations and in a fourth population with background exposure. However, positive findings were not observed overall in two other background-exposed populations. For testicular cancer, there were two studies with positive findings: one cohort study and a second ecological study that had limitations. For other cancer types, there were only sporadic positive findings in the informative studies (e.g. breast), and for all these other cancer types, the evidence was inadequate.

6.5.2 PFOS

The Group 2B evaluation for PFOS is based on strong mechanistic evidence. There is strong evidence that PFOS exhibits multiple key characteristics of carcinogens in exposed humans, human primary cells, and experimental systems. There is strong evidence that PFOS in exposed humans induces epigenetic alterations in the form of gene-specific methylation and cancer-related miRNAs. These effects are supported by evidence of epigenetic alterations in multiple experimental systems. In exposed humans, PFOS is immunosuppressive, increasing risk of infectious disease and decreasing vaccine response to diverse antigens. These effects are supported by evidence of immunosuppression in human primary cells and experimental systems. In human primary cells and experimental systems, PFOS modulates receptor-mediated effects and induces oxidative stress. Additionally, in experimental systems, PFOS alters cell proliferation, cell death, or nutrient supply.

In addition, the evidence for cancer in experimental animals was *limited*. Exposure to PFOS caused an increase in the incidence of an appropriate combination of benign and malignant neoplasms in one sex (female) of a single species (rat) in a study that complied with GLP. The evidence regarding cancer in humans was found to be *inadequate*, because among the relatively few available studies, positive findings were seen only sporadically and inconsistently for a few cancer sites (i.e. breast, testis, and thyroid).

LIST OF ABBREVIATIONS

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2-AAF 2-acetylaminofluorene

ACGIH American Conference of Governmental Industrial Hygienists

ACOX acyl-coenzyme A oxidase ACS American Cancer Society

ADME absorption, distribution, metabolism, or excretion

AFB₁ aflatoxin B₁

AFFF aqueous film-forming foam
AHR aryl hydrocarbon receptor
AOR adjusted odds ratios

APFO ammonium perfluorooctanoate

AR androgen receptor

ARE antioxidant responsive element

ASTM American Society for Testing and Materials

ATBC Alpha-Tocopherol, Beta-Carotene Cancer Prevention

ATP adenosine triphosphate

ATSDR Agency for Toxic Substances and Disease Registry

AUC area under the curve
BMI body mass index
BrdU bromodeoxyuridine
bw body weight

cAMP cyclic adenosine monophosphate CAR constitutive androstane receptor

CAT catalase CBD cannabidiol

CEPA Canadian Environmental Protection Act

CERCLA Comprehensive Environmental Response, Compensation, and Liability Act

CGA chlorogenic acid

CHDS Child Health and Development Studies

CHO Chinese hamster ovary
CI confidence interval
CIOB Chemicals in Our Bodies

CNBCSP Chinese National Breast Cancer Screening Program

CoA coenzyme A ConA concanavalin A

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CONTAM European Food Safety Authority Panel on Contaminants in the Food Chain

CpG 5'-C-phosphate-G-3'-dinucleotide

CPS Cancer Prevention Study
CRP C-reactive protein
CS collagen sandwich
CTS California Teachers Study
CV coefficient of variation
CYP cytochrome P450
DCF 2',7'-dichlorofluorescein

DCF-DA 2',7'-dichlorofluorescein diacetate

DCFH-DA 2',7'-dichlorodihydrofluorescein diacetate

DEN diethylnitrosamine
DFTJ Dongfeng-Tongji
dG 2'-deoxyguanosine
DHEA dehydroepiandrosterone

diPAP polyfluoroalkyl phosophate diester
DMBA 7,12-dimethylbenz[a]anthracene
DMR differentially methylated region

DMSO dimethyl sulfoxide
DNMT DNA methyltransferase
DoD Department of Defense

DoDSR Department of Defense Serum Repository

DOX doxycycline

DTH delayed-type hypersensitivity EC European Commission

ECG half-maximal effective concentration
ECA Environment and Childhood Asthma
ECCC Environment and Climate Change Canada

ECF electrochemical fluorination
ECHA European Chemicals Agency
EFSA European Food Safety Authority
eGFR estimated glomerular filtration rate
ELISA enzyme-linked immunosorbent assay

EPCRA Emergency Planning and Community Right-to-Know Act

ER estrogen receptor

ERS endoplasmic reticulum stress ESI electrospray ionization

N-EtFOSAA N-ethyl-perfluorooctane sulfonamido acetic acid

EU European Union

EWAS epigenome-wide association analysis study

FDR false discovery rate FMC Finnish Maternity Cohort

Fpg formamidopyrimidine-DNA glycosylase FSANZ Food Standards Australia New Zealand

FT3 free triiodothyronine FT4 free thyroxine FTOH fluorotelomer alcohol

GBCA Genetic and Biomarkers study for Childhood Asthma

GC gas chromatography GDP guanosine diphosphate

List of abbreviations

GF glomerular function
GFR glomerular filtration rate
GGT gamma-glutamyl transferase

GJIC gap junctional intercellular communication

GLP Good Laboratory Practice

GM geometric mean

GM-CSF granulocyte-macrophage colony-stimulating factor

GPx glutathione peroxidase

GRULAC Group of Latin America and the Caribbean

GSH glutathione

GSPE grape seed proanthocyanidin extract

GSR glutathione reductase
GSSG oxidized glutathione
GST glutathione S-transferase

γH2AX phosphorylated H2A histone family member X

HBM Human Biomonitoring

HBM4EU Human Biomonitoring for Europe

HCC hepatocellular carcinoma HETE hydroxyeicosatetraenoic acid

HFD high-fat diet

HGF hepatocyte growth factor
Hib Haemophilus influenza type b

HMC human mast cell

HMVEC human microvascular endothelial cells

HO-1 haem oxygenase 1

HOME Health Outcomes and Measures of the Environment

HPLC high-performance liquid chromatography

HR hazard ratio

HUVEC human umbilical vein endothelial cell
IARC International Agency for Research on Cancer
IC₅₀ half-maximal inhibitory concentration
ICC intraclass correlation coefficient

intractass correlation coeffic

IFN-γ interferon gamma Ig immunoglobulin

IKIDS Illinois Kids Development Study

IL interleukin

INHAND International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice

iNOS inducible nitric oxide synthase

INSR insulin receptor
i.p. intraperitoneal
IQR interquartile range
IRR incidence rate ratio

IsoF isofuran IsoP isoprostane

ITRC Interstate Technology and Regulatory Council

i.v. intravenous

JEM job-exposure matrix

KC key characteristic of carcinogens KEEP Korean Elderly Environmental Panel

KLH keyhole limpet haemocyanin

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LC₅₀ median lethal concentration

LC-MS/MS liquid chromatography-tandem mass spectrometry

L-FABP liver fatty acid-binding protein

LH luteinizing hormone

LINE-1 long interspersed nuclear element 1

LLE liquid-liquid extraction

LMIC low- or middle-income country

LOD limit of detection
LOQ limit of quantification
LOX lipoxygenase

LPS

LRTI lower respiratory tract infection
LTL leukocyte telomere length
LWBC Laizhou Wan (Bay) birth cohort
MCP-1 monocyte chemoattractant protein

lipopolysaccharide

MDA malondialdehyde
MDL method detection limit
MEC Multiethnic Cohort

MHC major histocompatibility complex

miRNA microRNA mRNA messenger RNA

MLQ method limit of quantification

MNNG N-methyl-N'-nitro-N-nitrosoguanidine

MRL minimum reporting level MRP multidrug resistance protein

MS mass spectrometry

MS/MS tandem mass spectrometry

MTT 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide

NAC N-acetylcysteine

NADPH nicotinamide adenine dinucleotide phosphate

NAFLD non-alcoholic fatty liver disease

NAR naringin; 4',5,7-trihydroxyflavonone-7-rhamnoglucoside NASEM National Academies of Sciences, Engineering, and Medicine

NDAA National Defense Authorization Act

NDI National Death Index

NESHAP National Emissions Standards for Hazardous Air Pollutants

NeuroP neuroprostane NGF nerve growth factor

NHANES National Health and Nutrition Examination Survey

NHL non-Hodgkin lymphoma

NHMRC National Health and Medical Research Council

NICHD National Institute of Child Health and Human Development

NK natural killer
NO nitric oxide
NOx nitrogen oxides
8-NO₂Gua 8-nitrosoguanine

NOAEL no observed adverse effect level

NPDES National Pollutant Discharge Elimination System NTCP Na+/taurocholate cotransporting polypeptide

NTP National Toxicology Program

List of abbreviations

OAT organic acid transporter

OATP organic anion transporting polypeptide

OCC Odense Child Cohort OCM organotypic culture model 8-OHdG 8-hydroxy-2'-deoxyguanosine

odds ratio OR

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8-oxodG 8-oxo-2'-deoxyguanosine PAH polycyclic aromatic hydrocarbon pancreatic intraepithelial neoplasia PanIN. PBDE polybrominated diphenyl ether **PBMC** peripheral blood mononuclear cells **PBPK** physiologically based pharmacokinetic

PCB polychlorinated biphenyl

PCDD 2,3,7,8-substituted polychlorinated dibenzodioxin PCDF 2,3,7,8-substituted polychlorinated dibenzofuran

PCNA proliferating cell nuclear antigen PCO palmitoyl coenzyme A oxidase PCR polymerase chain reaction PFAA perfluoroalkyl acid

PFAS perfluoroalkyl and polyfluoroalkyl substances

PFHpS perfluoroheptane sulfonate **PFHxS** perfluorohexanesulfonic acid perfluorononanoic acid PFNA **PFOA** perfluorooctanoic acid **PFOS** perfluorooctanesulfonic acid

PGF prostaglandin PHA phytohaemagglutinin PKA protein kinase A PKC protein kinase C

PLCO Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

PM particulate matter

particulate matter with diameter < 2.5 µm $PM_{2.5}$

POP persistent organic pollutant POSF perfluorooctane sulfonyl fluoride

PPAR peroxisome proliferator-activated receptor

ppb parts per billion

PPE personal protective equipment

ppm parts per million PR progesterone receptor polytetrafluoroethylene PTFE PUF polyurethane foam PWS public water systems PXR pregnane X receptor

qPCR quantitative polymerase chain reaction quick, easy, cheap, effective, rugged, safe QuEChERS RACK-1 receptor for activated C kinase 1

red blood cell RBC RCC renal cell carcinoma

RD human embryonal rhabdomyosarcoma cell line

REACH Registration, Evaluation, Authorisation and Restriction of Chemicals

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RL reporting limit RNA ribonucleic acid tRNA transfer RNA

RNS reactive nitrogen species ROS reactive oxygen species

RONS reactive oxygen and nitrogen species

RPE retinal pigment epithelial

RR rate ratio

RT-PCR reverse transcription-polymerase chain reaction

RSV respiratory syncytial virus

SCAP sterol regulatory element-binding protein cleavage-activating protein

SD standard deviation

SEER Surveillance, Epidemiology, and End Results

SEM systemic evidence map SHBG sex hormone-binding globulin SIR standardized incidence ratio **SMBCS** Sheyang Mini Birth Cohort Study SMR standardized mortality ratio SNUR Significant New Use Rules SOD superoxide dismutase SPE solid-phase extraction SRBC sheep red blood cell

StAR steroidogenic acute regulatory STEL short-term exposure limit

 $T_{1/2}$ half-life

TAC total antioxidant capacity
TAD total administered dose

TBARS thiobarbituric acid-reactive substance

TCA tricarboxylic acid

TCDD 2,3,7,8-tetrachlorodibenzo-p-dioxin

TCR T-cell receptor

TDAR T-cell-dependent antibody response

TDI tolerable daily intake
TFE tetrafluoroethylene

TGCT testicular germ cell tumour

TH thyroid hormone
TK toxicokinetic
TL telomere length

TNF-α tumour necrosis factor alpha

TNP trinitrophenyl

TPOAb thyroid peroxidase antibody
TR thyroid hormone receptor
TRI Toxics Release Inventory
TSH thyroid-stimulating hormone
TSCA Toxic Substances Control Act
TT3 total triiodothyronine

TT4 total thyroxine
TTR transthyretin

TWA time-weighted average TWI tolerable weekly intake

List of abbreviations

UBA Umweltbundesamt (German Environment Agency).
UCMR 3 Third Unregulated Contaminant Monitoring Rule

UK United Kingdom

UNEP United Nations Environment Programme

UPR unfolded protein response

US United States

USA United States of America

US EPA United States Environmental Protection Agency
US FDA United States Food and Drug Administration

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m d} & & {
m volume~of~distribution} \\ {
m vP} & & {
m very~persistent} \\ {
m WBC} & & {
m white~blood~cell} \\ {
m WT} & & {
m wildtype} \\ \end{array}$